REMARKS

In the Office Action under reply, claims 1-21 are pending. Claims 8-11 have been withdrawn from consideration as being drawn to non-elected subject matter. Claims 1-7, 12 and 18-21 stand rejected under 35 U.S.C. §112, first paragraph, as lacking enabling disclosure in the specification. Claims 13-17 have been objected to as dependent upon a rejected base claim but are indicated as otherwise allowable if rewritten in independent form.

Additionally the Examiner has objected to the Abstract as failing to convey the structural makeup of the Applicant's invention.

In the present amendment, claims 1, 6, 7, 18, and 21 have been amended and claim 2 has been cancelled. Thus, claims 1, 3-21 remain pending in the application. The Examiner's rejections and objections are addressed in part by the above-amendments and are otherwise traversed for the reasons presented below.

THE AMENDMENTS TO THE SPECIFICATION

The Abstract has been amended to incorporate the structure of Formula I.

The second Example 4 has been deleted.

Example 5 has been amended to incorporate the text of the now deleted second Example 4.

No new matter has been added.

THE AMENDMENTS TO THE CLAIMS

Claim 1 has been amended to reflect the election of the subject matter of Group I, i.e., the option for bridging of the R^3-R^8 groups has been deleted and the structure now reflects

that m is 1 and A is $-CR^9R^{10}$. Claim 2 has been cancelled to remove the resulting redundancy and claim 3 has been amended to correctly depend from claim 1.

Claim 1 has also been amended to clarify that R^1 is aryl or heteroaryl optionally substituted with 1 to 3 substituents selected from acetyl, alkyl, hydroxy, alkoxy, halogen, halogen substituted alkyl, phenyl, and phenyl substituted with acetyl, alkyl, alkoxy, hydroxy, halogen, or halogen substituted alkyl and that R^2 is heteroaryl optionally substituted with 1 to 3 substituents selected from acetyl, alkyl, hydroxy, alkoxy, halogen, halogen substituted alkyl, phenyl, and phenyl substituted with acetyl, alkyl, alkoxy, hydroxy, halogen, or halogen substituted alkyl. Support for this amendment is found in the claim as originally written.

Claim 6 has been amended to specify that R^1 is optionally substituted aryl. Support for this amendment is found in the claim as originally written.

Claim 7 have been amended to specify only that R^2 is optionally substituted benzothiazolyl or optionally substituted benzoxazolyl. Support for this amendment is found in the claim as originally written.

Claim 18 has been amended to incorporate the elements of claim 19. That is, claim 18 now recites a method of treating a disease state chosen from diabetes, damage to skeletal muscles resulting from trauma or shock and a cardiovascular disease selected from the group consisting of atrial arrhythmia, intermittent claudication, ventricular arrhythmia, Prinzmetal's (variant) angina, stable angina, unstable angina, congestive heart disease, and myocardial infarction.

Claim 19 has been amended to more clearly reflect it is drawn to a method wherein the disease state is a cardiovascular disease selected from selected from atrial arrhythmia, intermittent claudication, ventricular arrhythmia, Prinzmetal's (variant) angina, stable angina, unstable angina, congestive heart disease, and myocardial infarction.

Claim 21 has been amended to correctly incorporate the compound of claim 1.

It is noted that the cancellation of claim 2 is without prejudice, without intent to abandon and previously claimed subject matter, and without intent to acquiesce in any rejection of record.

No new matter has been added.

THE RESTRICTION REQUIREMENT

The Examiner required restriction of the claims as filed into four groups:

I. Claims 1-21, drawn to compounds, composition, and uses wherein m = 1 and R^3-R^8 do not form a ring;

II. Claims 1, 2, and 18-21, drawn to compounds, composition, and uses wherein m = 1 and R^3-R^8 do form a ring;

III. Claims 1-7, 12, and 18-21, drawn to compounds, composition, and uses wherein m = 2 and R^3-R^8 do not form a ring; and

IV. Claims 1, 2, and 18-21, drawn to compounds, composition, and uses wherein m = 2 and R^3-R^8 do form a ring.

In a telephone conversation with the Examiner on September 26, 2005, Applicants made a provisional election of the claims of Group I with the right to traverse. Applicants hereby confirm the election without traverse.

During the telephone conversation, the Examiner additionally requested that a species be selected for initial examination and the undersigned attorney elected the species wherein R^2 is benzothiazolyl.

Based on Applicants election of species, the Examiner has subjected the claims to further restriction, requiring that R^1 and R^2 both be heteroaryl. Applicants respectfully traverse this restriction on the ground that there would be no serious burden on the Office should R^1 and R^2 be as currently claimed, that is, R^1 can be either aryl or heteroaryl while R^2 is heteroaryl. Applicants refer the Examiner to M.P.E.P. §803, wherein it is stated that "[i]f

the search and examination of an entire application can be made without serious burden, the examiner **must** examine it on the merits...."

Furthermore, applicants submit that restriction of the claims to those compounds wherein R^1 and R^2 are both heteroaryl is inconsistent with *In re Weber,* 580 F.2d 455, 198 USPQ 328 (CCPA) in which the court articulated the general proposition that:

> [A]n applicant has a right to have *each* claim examined on the merits. If an applicant submits a number of claims, it may well be that pursuant to a proper restriction requirement, those claims will be dispersed to a number of applications. Such action would not affect the right of the applicant eventually to have each of the claims examined in the form he considers to best define his invention. If, however, a single claim is required to be divided up and presented in several applications, that claim would never be considered on its merits. The totality of the resulting fragmentary claims would not necessarily be the equivalent of the original claim. Further, since the subgenera would be defined by the examiner rather than by the applicant, it is not inconceivable that a number of the fragments would not be described in the specification. *Id.* At 331. (Emphasis in original).

In view of the above, applicants submit that R^1 should not be restricted to only heteroaryl moieties.

THE OBJECTION TO THE SPECIFICATION

The Examiner objected to the Abstract of the Disclosure as it "does not convey the structural makeup of the applicants' invention". In response, Applicants have amended the Abstract to incorporate the structure of Formula I.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The Examiner has rejected claims 1-7, 12, and 18 to 21 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement and asserts that the claims encompass subject matter that was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Applicants

respectfully disagree and submit that, as the specification discloses a vast number of compounds having a wide variety of R^1 aryl and heteroaryl moieties and R^2 heteroaryl moieties, claims to such aryl and heteroaryl compounds are clearly enabled.

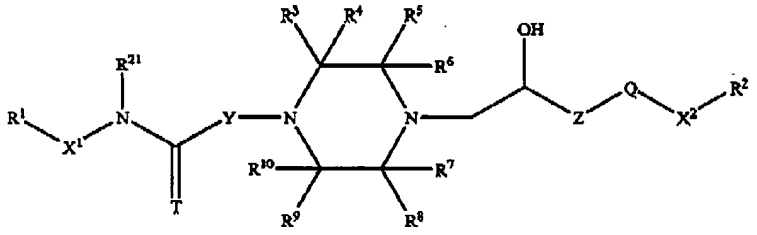
As amended, independent claim 1 recites disubstituted piperazine compounds having terminal R^1 moieties that are aryl or heteroaryl optionally substituted with 1 to 3 substituents selected from acetyl, alkyl, hydroxy, alkoxy, halogen, halogen substituted alkyl, phenyl, and phenyl substituted with acetyl, alkyl, alkoxy, hydroxy, halogen, or halogen substituted alkyl and R^2 moieties that are heteroaryl optionally substituted with 1 to 3 substituents selected from acetyl, alkyl, hydroxy, alkoxy, halogen, halogen substituted alkyl, phenyl, and phenyl substituted with acetyl, alkyl, alkoxy, hydroxy, halogen, or halogen substituted alkyl. The Examiner has stated that the only R^1 heteroaryl moieties made and tested are thiazole, quinoline, and carbazole and that the only substitution made to the respective R^1/R^2 moieties is alkyl, phenyl, and chlorophenyl. Applicants believe that the Examiner has based this conclusion on the listing provided in Example 21 of the application wherein a few representative compounds are presented along with NMR and biological test data.

In contrast to the limited number of compounds presented in Example 21, Applicants respectfully direct the Examiner to Example 4, on page 39 to 54, and Example through page 54, wherein the making of over 200 compounds is taught. As the Examiner will see, a wide variety of compounds having different R^1/R^2 heteroaryl and aryl were made and one of ordinary skill in the art would have no difficulty in adapting the teaching provided therein to produce any of the other compounds falling within the scope of claim 1. Applicants remind the Examiner that an Applicant is not required to reduce every compound claimed to practice and that a claim should not be limited to only those compounds provided in the working examples.

In bringing a rejection based on a lack of enablement, an examiner is required to establish a reasonable basis to question the enablement provided for the claimed invention *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is

not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of **35 U.S.C. 112**, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

That is to say, so long as the specification teaches how to make and use the subject matter of the invention to a degree that corresponds with the extent to which to the subject matter is defined and described in the claims, the claims are enabled. To correctly asses if this requirement has been satisfied, one must first look at just how the subject matter is defined and described in the claims. In this case, the claims recite compounds having the structure



wherein:

R^1 is aryl or heteroaryl optionally substituted with 1 to 3 substituents selected from acetyl, alkyl, hydroxy, alkoxy, halogen, halogen substituted alkyl, phenyl, and phenyl substituted with acetyl, alkyl, alkoxy, hydroxy, halogen, or halogen substituted alkyl; and

R^2 is heteroaryl optionally substituted with 1 to 3 substituents selected from acetyl, alkyl, hydroxy, alkoxy, halogen, halogen substituted alkyl, phenyl, and phenyl substituted with acetyl, alkyl, alkoxy, hydroxy, halogen, or halogen substituted alkyl.

The next step in determining enablement is to asses whether the specification teaches how to make and use the subject matter of the invention to a degree that corresponds with the extent to which to the subject matter is defined and described in the claims. Applicants direct the Examiner to pages 17 to 26 of the specification which presents detailed

descriptions of various methods and processes that can be used to produce the compounds of the claim 1 from commercially available starting material. Applicants also wish to point the Examiner to Examples 11-20 which teach methods of formulating the compounds of the invention into pharmaceutical compositions and to Examples 21-29 which teach methods of testing and assessing the biological activity of the compounds.

Applicants submit that the chemistry involved in these reactions is neither complicated nor unpredictable, generally involving alkylation of an amine using either a halogen leaving group or an epoxide ring opening addition, all of which are well within the abilities and understanding of one of ordinary skill in the art. The size of the R^1 or R^2 heteroaryl or aryl ring, the number and position of the various hetero atoms or substituents, would not unduly complicate the described reactions and would not alter the inherent predictability of the chemistry involved. Similarly, the methods used in assessing the biological activity are also well known and routine in nature.

As the Examiner seems to be focusing her rejection on variety of compounds provided by the definitions of R^1 and R^2 applicants will focus their comments here as well. As discussed above, the R^1 substituents can be aryl or heteroaryl while the R^2 substituents are heteroaryl. The specific R^1/R^2 substituents themselves can only be further modified by a limited number of substituents. Applicants agree that the claim encompasses a large number of compounds; however, applicants do not agree that the number of compounds claimed exceeds the scope of enabling disclosure in the specification or that undue experimentation is required to determine the meets and bounds of the claimed subject matter. The question of whether undue experimentation is required may be address by an analysis of the criteria set forth in *In re Wands*. Each of the Wands factors will be discussed separately below.

A. The Breadth of the Claims

Applicants agree with the Examiner that a large number of compounds fall within the scope of the pending claims. Applicants wish to point out, however, that the size and number of rings in the R^1 and R^2 substituents are clearly defined in the specification and

that the pending claims have been amended to limit the type and number of possible substituents to 1 to 3 substituents selected from acetyl, alkyl, hydroxy, alkoxy, halogen, halogen substituted alkyl, phenyl, and phenyl substituted with acetyl, alkyl, alkoxy, hydroxy, halogen, or halogen substituted alkyl. Applicants submit that as the R^1 and R^2 moieties and their possible substituents are clearly defined, this factor alone does not render the claims non-enabled.

B. The Nature of the Invention

The nature of the invention is disubstituted heterocyclic compounds, herein currently claimed as disubstituted piperazine compounds, that are believed to act as fatty acid oxidation inhibitors. Numerous patents has issued on these type of compounds, many by the assignee of the current application.

C. The State of the Prior Art

While the Examiner has acknowledged that similar compounds are known in the art having similar backbone and for the same activity, she has concluded that, given the many structural permutations of encompassed by the currently pending claims, the prior art does not "evidence" the pending claims. Applicants are somewhat unclear about the Examiners meaning and request clarification. Furthermore, Applicant's submit that the prior art is well defined with respect to both the chemistry used to prepare the claimed compounds and the methods used to analyze and asses the individual compounds.

D. The Level of Ordinary Skill in the Art

Applicants believe that it is clear that the level of one of ordinary skill is high with respect to the synthetic portion of the invention. Applicants submit that those of ordinary skill in the art are of PhD levels of education with significant experience in the field. As such, this factor weighs in support of patentability.

E. The Level of Predictability

Applicants submit that the level of predictability is high with respect to the synthetic portion of the invention. Applicants also strongly believe that the level of predictability with respect to the specific medicinal activity is also high. Given the present understanding of structure activity relationships (SAR), the ability of one structurally related family of compounds to have a predictable effect on a specific receptor subtype forms the basis for a significant portion of small molecule pharmaceutical research.

F. The Amount of Direction Provided

The specification clearly teaches how to make the compounds. Given that the level of ordinary skill in the art is high with respect to the synthetic methods used, the guidance provided in the specification on how to make the compound is surely sufficient.

Similarly, the specification also clearly teaches how to test the compounds to establish and verify their individual ability to inhibit fatty acid oxidation. Once again, given the level of skill of the average Ph.D. biologist, there would be no difficulty running the assays described in the Experimental section of the specification. Such test are routine and well within the abilities of the average pharmaceutical biology lab technician.

G. The Existence of Working Examples

The Examiner has stated that there is no test data presented. Applicants disagree. As discussed above, Example 21 presents sample date for a representative number of compounds having a variety of different R^1 and R^2 substituents. While Applicants have not provided test data for all of the 200 plus compound synthesized in the specification, Applicants wish to remind the Examiner that there is no requirement in U.S. Patent Law for Applicants to provide any test data. "Where assertions of utility are believable on their face and straight forward, and no reason or authority in variance has been advanced, the disclosed utility must be accepted as accurate." In re Bundy, 642 F.2d 430, 209 U.S.P.Q. 18 (CCPA 1981). Applicants has provided data for representative compounds and have stated

that the remainder of the 200 plus compounds specifically recited were tested and found the have the requisite biological activity. Unless the Examiner has some reason to doubt Applicants assertions, the number and variety of compounds prepared and tested clearly support enablement of the claims as currently pending.

H. The Quantity of Experimentation

While the Examiner has not specifically alleged that the quantity of experimentation needed to make or use the invention based upon the disclosure is deemed to be , Applicants submit that the reaction schemes and examples provided in the specification show precisely how the compounds of the invention can be made. One of ordinary skill would have no difficulty in adapting the reaction schemes and the working examples 1-10 in order to arrive at any compound within the scope of the invention.

Based on an assessment of the Wands factors, the compound claims are not overly broad and the level of skill, predictability, and art are high, no undue experimentation is required and claim 1 and all claims dependent thereupon are fully enabled by the specification.. Reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is in order and is respectfully requested.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The Examiner has additionally rejected method claim 18 as lacking enabling disclosure for the treatment of all cardiovascular diseases. While not necessarily agreeing with the Examiner's position and in the interest of expediting prosecution, Applicants have amended claim 18 to incorporate the specific cardiovascular disease recited in claim 19. As the Examiner has indicated that the method claims for treating the specific condition recited in claim 19 are enabled by the specification, Applicants submit that the rejection is now moot and respectfully request its withdrawal.

THE OBJECTION TO THE CLAIMS

The Examiner has indicated that claims 13-17 are objected to, but would be allowable if rewritten in independent form. Applicants respectfully submit that the above amendments and accompanying remarks render the claim objections moot, and all claims are now in a condition for allowance.

CONCLUSION

For the foregoing reasons, Applicants submit that the claims are in condition for allowance. A Notice of Allowance is requested, and a prompt mailing thereof would be much appreciated.

Should the Examiner have any questions, he is invited to contact the undersigned attorney at (650) 384-8755.

Respectfully submitted,

Date: 1/9/06

By: _____

J. Elin Hartrum
Reg. No. 43,663
Customer No. 27716

CV Therapeutics, Inc.
3172 Porter Drive
Palo Alto, CA 94304
Phone: (650) 384-8755
Fax: (650) 475-0359

S:\LEGALCVT\Patent\Docs\02-0175\02-175-US\Resp to 10-12-05 OA.doc